PCT/IB2004/00 3278

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Provisional Specification filed on 20.02.2004 of the extract of Patent Application No. 136/CHE/2004 by M/S National Centre for Biological Sciences , Tata Institute of Fundamental Research, UAS-GKVK Campus, Bellary Road, Bangalore-560 065,Karnataka, India, an Indian Company.

.....

.....**In witness thereof**

I have hereunto set my hand

Dated this the 25th day of October, 2004
3rd day of Kartica, 1926 (Saka)

M.S.V

(M.S.VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
Guna Complex, 4th Floor, Annex.II
No.443, Anna Salai, Teynampet,
Chennai - 600 018

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

20/2

FORM 1

THE PATENTS ACT 1970
(39 OF 1970)

APPLICATION FOR GRANT OF PATENT
[See Sections 5(2), 7, 54 and 135 and rule 33a]

1. I/We,

(a) National Centre for Biological Sciences
Tata Institute of Fundamental Research
UAS-GKVK Campus
Bellary Road
Bangalore – 560 065

2. hereby declare –
   a) that we are in possession of an invention titled
   "A NOVEL POTASSIUM CHANNEL ACTIVATOR PEPTIDE"

   b) that a provisional specification relating to this invention is filed with this application.

   c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventor(s) of the said invention are

   1. Prof. K. S. Krishnan, National Centre for Biological Sciences, Tata Institute of Fundamental Research, Bangalore – 560 065, an Indian National
   2. Prof. P. Balaram, Indian Institute of Science, Bangalore – 560 012, an Indian National

4. We claim the priority from the application(s) filed in convention countries particulars of which are as follows:

   a) Not applicable
   b) Not applicable
   c) Not applicable
   d) Not applicable

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant / patentee:

   a) Not applicable
   b) Not applicable
   c) Not applicable

K. Vijayan

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on this fifteenth day of September 2003, under section 16 of the Act

   a) Not applicable
   b) Not applicable
   c) Not applicable

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

   Senior Administrative Officer
   National Centre for Biological Sciences
   Tata Institute of Fundamental Research
   UAS-GKVK Campus, Bellary Road
   Bangalore – 560 065

   Ph: +91-80-3636729
   Email: tms@ncbs.res.in

9. Following declaration was given by the inventor(s) or applicants(s) in the convention country:

   I/We, the true and first inventor(s) for this invention or the applicant(s) in the convention country declare that the applicant(s) herein is our assignee or legal representative.

P. Balaram

Prof. P. BALARAM

Prof. K. S. KRISHNAN

10. That to the best of our knowledge, information and belief that fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. The following are the attachments with the application:

    a. Provisional specification in ~~triplicate~~ duplicate on Form 2
    b. Statement & undertaking on Form 3

KC Uyappa

c. Demand draft of the Central Bank of India for Rs.3,000/- (Rupees Three Thousand only) bearing No. 030695 dated 19th February 2004 drawn on Chennai.

Fee Rs.3,000/- (Rupees Three Thousand only) vide demand draft bearing No. 030695 dated 19th February 2004 drawn on Chennai.

We request that a patent may be granted to us for the said invention.

Dated this Nineteenth day of February 2004.

K. VijayRaghavan
Centre Director
NCBS-TIFR

To
The Controller of Patents
The Patent Office
CHENNAI

FORM 2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION:
(see Section 10, Rule 13)

A NOVEL POTASSIUM CHANNEL ACTIVATOR PEPTIDE

We, **National Centre for Biological Sciences, Tata Institute of Fundamental Research, UAS-GKVK Campus, Bangalore – 560 065, INDIA**

The following specification particularly describes and ascertains the nature of this invention:

Field of invention

This invention relates to the field of a potassium channel activating molecules that will have utility in the field of human medicine.

Prior art

The venoms of cone snails are primarily a complex mixture of biologically active peptides, which target a diverse range of ion channels and receptors, permitting rapid immobilization of prey. The polypeptide toxins acting in concert ("a cabal") simultaneously target several critical signaling pathways in the central nervous system of worms, fishes and molluscs. The ability of these peptides to act as selective ligands for receptors and channels in the mammalian nervous system has triggered considerable interest in their chemistry and neuropharmacology. Small, disulfide bonded polypeptides, conotoxins, have been the most extensively studied components of cone snail venom.

Some reports of biologically active acyclic peptides have also appeared. These include, the conantokins, a gamma carboxy glutamate containing peptide, contulakin, a neurotensin receptor antagonist and conorfamide, which appears to act in a manner similar to the FMRF-amide neuropeptide family. The molecular diversity of K_+ channels is larger than any other group of ion channels, with more than 80 different genes and many splice variants. The diversity is strikingly observed in the central nervous system, with numerous subtypes of neurons expressing a unique set of potassium channels. The voltage gated potassium channels are responsible for the repolarization of the action potential in neurons. In this study, we describe, the characterization of a novel 13 residue peptide Mo1659 isolated from the venom of *Conus monile*, a vermivorous snail found off the south east coast of India, which targets non- inactivating voltage dependent K_+ channels. The mass spectrometrically determined sequence FHGGSWYRFPWGY-NH_2 is remarkable in that it contains a high proportion of aromatic amino acids and is completely devoid of the common hydrophobic, aliphatic amino acids and disulfide bridges.

NATURE OF INVENTION

A novel 13-residue peptide Mo1659 has been isolated from the venom of a vermivorous cone snail, *Conus monile*. HPLC fractions of the venom extract yielded an intense UV absorbing fraction with a mass of 1659 Da. *De novo* sequencing using both matrix assisted laser desorption and ionization and electrospray MS/MS methods together with analysis of proteolytic fragments successfully yielded the amino acid sequence, FHGGSWYRFPWGY-NH_2. This was further confirmed by comparison with the chemically synthesized peptide and by conventional Edman sequencing. Mo1659 has an unusual sequence with a preponderance of aromatic residues and the absence of apolar, aliphatic residues like Ala, Val, Leu, Ile. Mo1659 has no disulfide bridges distinguishing it from the conotoxins and bears no sequence similarity with any of the acyclic peptides isolated thus far from the venom of cone snails. Electrophysiological studies on the effect of Mo1659 on measured currents in dorsal root ganglion neurons suggest that the peptide targets non-inactivating voltage dependent potassium channels.

This peptide is likely to be very useful in the directed treatment of a range of neurophysiological and neurological disorders such as those seen in schizophrenia, epilepsy, bipolar disorder and in syndromes that affect the nervous system.

Dated this Nineteenth day of February 2004.

Centre Director
NCBS-TIFR

To,
The Controller of Patents
The Patent Office
CHENNAI

Abstract

A novel 13-residue peptide Mo1659 has been isolated from the venom of a vermivorous cone snail, *Conus monile*. HPLC fractions of the venom extract yielded an intense UV absorbing fraction with a mass of 1659 Da. *De novo* sequencing using both matrix assisted laser desorption and ionization and electrospray MS/MS methods together with analysis of proteolytic fragments successfully yielded the amino acid sequence, FHGGSWYRFPWGY-NH_2. This was further confirmed by comparison with the chemically synthesized peptide and by conventional Edman sequencing. Mo1659 has an unusual sequence with a preponderance of aromatic residues and the absence of apolar, aliphatic residues like Ala, Val, Leu, Ile. Mo1659 has no disulfide bridges distinguishing it from the conotoxins and bears no sequence similarity with any of the acyclic peptides isolated thus far from the venom of cone snails. Electrophysiological studies on the effect of Mo1659 on measured currents in dorsal root ganglion neurons suggest that the peptide targets non-inactivating voltage dependent potassium channels.